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PRIORITY DOCUMENT

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Signed Stephen Hordley

Dated 29 April 2003

GB 0206448.3

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

IONIX PHARMACEUTICALS LTD,
185 Cambridge Science Park,
Milton Road,
Cambridge,
CB4 0GA,
United Kingdom

Incorporated in the United Kingdom,

[ADP No. 08304891001]

and

WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTRE LTD,
Albert Einstein Centre,
Nottingham Science & Technology Park,
University Boulevard,
NOTTINGHAM,
NG7 2TN,
United Kingdom

Incorporated in the United Kingdom,

[ADP No. 07657521001]

Patents Form 1/77

Patents Act 1977
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The Patent Office

19MAR02 E704807-1 D10055
P01/7700 0.00-0206448.3

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Request for grant of a patent

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The Patent Office

Cardiff Road
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1.	Your reference	P0005
		19 MAR 200
2.	Patent application number *(The Patent Office will fill in this part)*	0206448.3
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Ionix Pharmaceuticals Ltd 185 Cambridge Science Park Milton Road Cambridge, CB4 0GA SECTION 30 (1977 ACT) APPLICATION FILED 17/3/03
	Patents ADP number *(if you know it)*	8304891001
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4.	Title of the invention	Analgesics
5.	Name of your agent *(if you have one)*	~~Dr Lyn Leaper~~ J.A KEMP & Co
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	~~Stratagem IPM Ltd The Old Rectory Nedging Tye Ipswich IP7 7HQ~~ 14 SOUTH SQUARE GRAY'S INN LONDON WC1R 5JJ. FS1/77 HP9.
	Patents ADP number *(if you know it)*	~~7995780001~~

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

0031914 19-Mar-02

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	27
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I / We request the grant of a patent on the basis of this application.

Signature Date 19 Mar. 02

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr Lyn Leaper 01353 698235 Lyn Leaper

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b) *Write your answers in capital letters using black ink or you may type them.*

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e) *Once you have filled in the form you must remember to sign and date it.*

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ANALGESICS

Field of the Invention

The invention relates to intranasal analgesic compositions and devices comprising in combination an analgesic component and a delivery agent and to analgesic methods based thereon. In particular, the invention relates to intranasal analgesics and analgesia whereby on introduction into the nasal cavity of a patient to be treated the analgesic component is delivered to the bloodstream by the delivery agent to produce rapid onset and prolonged analgesia.

Background to the Invention

Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience in association with actual or potential tissue damage". Pain can be acute or chronic. Acute pain is temporary. It can last a few seconds or longer but wanes as healing occurs. Acute pain usually starts suddenly, may be sharp, and often triggers visible bodily reactions such as sweating and elevation of blood pressure. Acute pain is generally a signal of rapid-onset injury to the body (commonly surgery, burns, cuts and fractures) or intense smooth muscle activity (as in colic, headache or ischaemia). Chronic pain ranges from mild to severe and occurs over a long time period (often weeks, months or years): in some cases it may last indefinitely. Acute pain can rapidly evolve into chronic pain, since some injuries cause plasticity changes in the nervous system and induce neuronal gene expression changes responsible for generating chronic pain within 30 min after injury.

Pain can also be classified on the basis of pathophysiology into: nociceptive (also called 'physiological' or 'ouch' pain) and pathological. Pathological pain may be further subdivided into inflammatory and neuropathic. Nociceptive pain results from the stimulation of peripheral nociceptors and direct transmission via the normal pain pathway to the sensory cortex; it is particularly important in acute pain like post-operative or trauma pain. Inflammatory pain results from stimulation of peripheral nociceptors by a variety of inflammatory mediators and can result in longer-term sensitisation changes. Neuropathic pain results from damage to neurones, either in the periphery or in the

central nervous system (CNS), and can be initiated either as a result of changes in peripheral inputs or entirely through plasticity changes in the CNS. Many neuropathic pain syndromes involve both central and peripheral components. Neurone damage leads to longer-term sensitisation changes both on peripheral axons (e.g. increased expression of certain ion channels) and in the central nervous system (e.g. NMDA receptor-mediated 'wind-up', changes in gene expression and morphological changes).

Pain may also be classified on the basis of aetiology. Cancer pain, which can be caused by the disease itself or by its treatment, is common in cancer patients. Approximately 30% to 50% of people with cancer experience pain while undergoing treatment and 70% to 90% of people with advanced cancer experience pain.

Post-operative pain varies in severity and characteristics between different types of surgery. Each surgical procedure can be considered as a specific pain model. Pain after thoracic surgery is amongst the most severe seen in the postoperative period and is difficult to treat efficiently and safely. Treatment for pain is also an important aspect of post-operative recovery in abdominal surgery, orthopaedic surgery and outpatient surgery (including dental and minor surgery).

Inflammatory pain is associated with tissue inflammation. An important class of inflammatory pain is that associated with arthritis. Arthritis is a group of more than a hundred rheumatic diseases that can cause pain, stiffness and swelling in the joints. These diseases may affect not only the joints but also other parts of the body, including associated tissues such as muscles, bones, tendons and ligaments and certain organs. Two of the most common forms of arthritis that usually causes chronic pain are osteoarthritis and rheumatoid arthritis.

Back pain usually affects the lower part of the back. It is described as acute (if it has lasted less than six weeks), sub-acute (if it has lasted six to twelve weeks) and chronic (if it has lasted more than 12 weeks).

Myocardial ischaemic and infarction pain is usually described as pressing, squeezing, or weight-like. The pain usually radiates from the centre of the torso in the distribution of the lower cervical nerves and may therefore be felt in the neck, lower jaw or either shoulder or arm (most commonly the left shoulder and left arm).

<u>Analgesia and analgesics</u>

There is a continuing need for medications able to relieve or eliminate pain (known as analgesics). Analgesia also plays an essential role in anesthesia, providing pre- and post-operative therapy as well as contributing to anesthesia itself. Thus, analgesia is seen as one of three components of "balanced anesthesia", with unconsciousness and muscle relaxation being the other two. During unconsciousness, although pain is not experienced, nociception and autonomic responses still occur and so the analgesia benefits the patient: prevention of nociceptive input to the CNS during surgery contributes to post-operative analgesia by preventing sensitisation of the CNS.

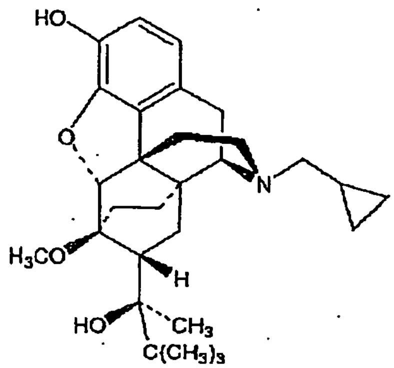
Analgesics can be classified into two broad classes: opioids and non-opioids.

Opioid analgesics

The term opioid (or opiate) defines drugs with morphine-like properties. Opioids can be sub-classified on the basis of their receptor specificity. *Mu*-agonist opioids provide intense analgesia. These opioids can be long-acting (e.g. methadone) or short-acting (e.g. remifentanil).

Mixed agonist/antagonist opioids (e.g. butorphanol and buprenorphine) are partial agonists (the former at *mu* and kappa receptors and the latter at the *mu* receptor), and can produce good quality analgesia. They produce less respiratory depression and constipation than high efficacy *mu* agonists..

Buprenorphine (CAS RN 52485-79-7; [5α,7α(*S*)]-17-(Cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol) has the formula:



The hydrochloride is also active (CAS RN 53152-21-9).

Buprenorphine is a highly lipophilic derivative of thebaine. It is a partial *mu* agonist and mediates analgesia at the *mu* opioid receptor. Buprenorphine produces a similar maximum analgesic effect to full *mu* agonists such as morphine in animal models of pain, and although it may have a ceiling effect in certain pain types in man, it has been shown to produce good quality analgesia of similar efficacy to morphine in most clinical situations including severe pain. An unusual property of buprenorphine observed in *in vitro* studies is its very slow rate of dissociation from its receptor.

As a class, opioids are associated with a number of undesirable side-effects, including respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention and hypotension. The development of tolerance and the risk of chemical dependence and abuse are further problems. Buprenorphine, however, is unusual in exhibiting a low maximum effect for respiratory depression and also a bell-shaped dose response curve, where the effect first increases with larger doses, reaches a ceiling and then diminishes as the dosage is further increased, which makes it a safer drug than morphine, where respiratory depression will ultimately lead to death. Buprenorphine has also been shown to have a lower incidence of other side-effects like constipation in man, and it has a lower abuse potential than full *mu* agonists.

Other opioid analgesics include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, butorphanol, clonitazene, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene,

dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalbuphine, nalorphine, naloxone, naltrexone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, profadol, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine and tramadol. Also included are esters, salts and mixtures of any of the foregoing.

Thus, opioid analgesics for use in the invention include *mu*- and/or kappa mixed agonists/antagonists, *mu*-antagonist combinations and esters, salts and mixtures thereof.

The salts for use in the invention may be pharmaceutically acceptable salts, including pharmaceutically acceptable acid addition salts. Examples include hydrochloride salts (for example the hydrochloride salts of nalbuphine, profadol, buprenorphine, morphine, pentazocine, naloxone and nalorphine) as well as levorphanol tartrate, nalorphine hydrobromide, levallorphan tartrate, morphine sulfate, butorphanol tartrate, pentazocine lactate and phenazocine hydrobromide.

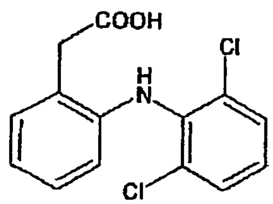
Non-opioid analgesics and NSAIDs

It is partly because of the side effects of opioids that interest has grown in the use of non-opioid analgesics. Much of this interest has focused on the large class of non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs include compounds such as the cyclooxygenase (COX) COX-1 and COX-2 inhibitors. Specific examples include ibuprofen, flurbiprofen, diclofenac, indomethacin, piroxicam, ketoprofen, etodolac, diflusinal, meloxicam, aceclofenac, fenoprofen, naproxen, tiaprofenic acid , tolmetin, celecoxib and rofecoxib..

Diclofenac is available in several different forms, described below:

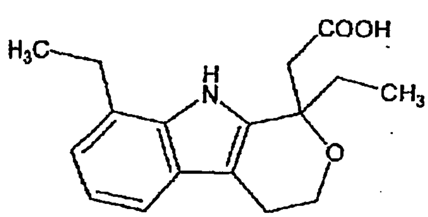
Diclofenac (CAS RN 15307-86-5; 2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid) has the formula:



Diclofenac Sodium (CAS RN 15307-79-60; 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid sodium salt) is sold under the following trade marks: Allorvan, Benfofen, Dealgic, Deflamat, Delphinac, Diclomax, Diclometin, Dichlophlogont, Diclo-Puren, Dicloreum, Diclo-Spondyril, Dolobasan, Duravolten, Ecofenac, Effekton, Lexobene, Motifene, Neriodin, Novapirina, Primofenac, Prophenatin, Rewodina, Rhumalgan, Trabona, Tsudohmin, Valetan, Voldal, Voltaren and Xenid.

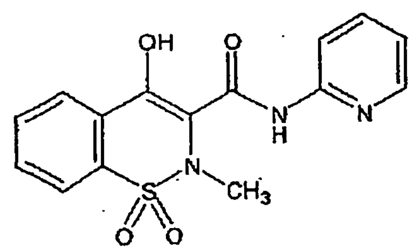
Diclofenac Potassium (CAS RN 15307-81-0; 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid potassium salt) is also known as Cataflam™.

Etodolac (CAS RN 41340-25-4; 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid) has the formula:



It is sold under the following trade marks: Etogesic, Lodine, Tedolan and Ultradol.

Piroxicam (CAS RN 36322-90-4; 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) has the formula



It is sold under the following trade marks: Sinartrol, Zelis, Zen, Brexin, Cicladol and Cycladol.

As a class, NSAIDS have anti-inflammatory actions and are effective on pain associated with the release of prostaglandins (PG) and other mediators of inflammation. They act by blocking the action of cyclooxygenase (COX), which converts arachidonic acid to eicosanoids. The eicosanoids include the prostanoids, prostacyclin (PGI_2), PG-E_2 and the thromboxanes.

There are at least two COX enzymes: a constitutively-expressed COX-1 responsible for producing homeostatic prostaglandin and thromboxane mediators and an inducible COX-2 that is produced in large quantities in response to stimuli such as infection and inflammation.

Since the prostaglandins and thromboxanes mediate a number of homeostatic and protective mechanisms, toxic side effects often arise from the use of NSAIDs as a result of disruption of these mechanisms. These include clotting disorders (leading to prolonged bleeding times) and gastric irritation (including ulceration). NSAIDs may also cause salt and water retention and may therefore exacerbate hypertension. They may also be teratogenic at high doses during pregnancy and as a result they are contra-indicated in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, a

recurrent history of gastrointestinal lesions, gastrointestinal bleeding, coagulation disorders (such as aenemia, hypoprothrombinemia and haemophilia), kidney diseases and in patients about to undergo surgery or taking anticoagulants.

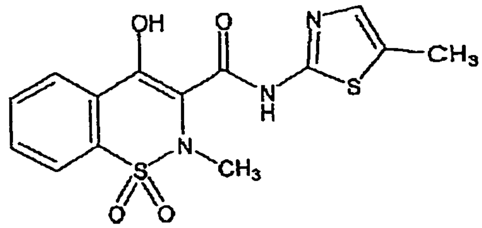
The NSAIDs are associated with a number of adverse effects on the kidneys, although most are rare. The kidney produces PGI_2, PGE_2 and some $PGF_{2\alpha}$. These are involved in local modulation of renal blood flow, glomerular filtration rate, renin release, the concentrating mechanism for urine and the excretion of sodium and potassium. The unwanted effects of NSAIDs result from the decrease in production of the prostaglandins and are summarized below:

1. Acute reversible/vasomotor renal failure.
2. Interference with the renal excretion of water, sodium and potassium.
3. Interference with antihypertensive therapy and diuretic therapy.
4. Acute interstitial nephritis with or without renal failure.
5. Nephrotic syndrome with or without interstitial nephritis and renal failure.
6. Chronic renal injury ("analgesic nephropathy").

There is great interest in the development of NSAIDs that are COX-2 specific, since such drugs would be expected to permit the treatment of inflammation and pain without affecting COX-1-mediated gastrointestinal protection. However, COX-2 inhibitors still show the renal and cardiac effects of non-selective NSAIDs.

Currently, celecoxib and rofecoxib are the most COX-2 selective agents available for clinical use but meloxicam and etodolac show greater selectivity than other NSAIDs which are COX-1 selective.

Meloxicam (CAS RN 71125-38-7; 4-Hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) has the formula:



However, as described above COX-2 specificity does not obviate all toxic NSAID side-effects, probably because COX-2 appears to share a role in normal homeostatic functions with COX-1. Moreover, at least in cases of chronic pain and inflammation, COX-1 may be as important as COX-2.

There are other limitations on the use of NSAIDs as analgesics, since they exhibit a very low ceiling effect that limits the degree of analgesia obtainable and often renders their use alone insufficient to treat intense pain (such as that associated with post-operative recovery or late stage osteoarthritis).

Other non-opiate analgesics include tricyclic antidepressants (e.g. amitryptiline), anticonvulsants (e.g. gabapentin) and antimigraine compounds (e.g. sumatriptan and naratriptan).

Administration of Analgesics and Pain Management

Ideally, pain relief should follow immediately upon administration of the analgesic and the relief be maintained for an extended period that is at least long enough to permit normal unbroken sleep patterns and avoid complicated dosage regimes.

In practice, however, the dynamics of pain relief obtained with current analgesic administration technologies does not meet these ideals. While rapid onset pain relief can be achieved by intravenous injection, this mode of administration cannot in general be

carried out by the patient and so is relatively expensive and inconvenient. Moreover, intravenous injection is generally associated with rapid offset of pain relief as the circulating analgesic is cleared from the plasma: prolonged analgesia requires multiple injections which is inconvenient and expensive. Intravenous injection is also usually associated with relatively high C_{max} values, which can trigger (or amplify) any side effects associated with the analgesic.

While alternative technologies (including intramuscular injection and inhalation) have been developed for effecting rapid onset analgesia, these all rely upon rapid delivery of the bulk of the analgesic dose into the blood system and so suffer from the same rapid offset problems associated with intravenous injection.

Attempts have been made to obviate such problems by providing pumped analgesic into the blood supply *via* a patient-controlled quick-dose pump. While this apparatus has the potential for long-term effective pain management, it is expensive, does not permit ambulation, requires extensive monitoring and may interfere with normal sleep patterns (depending on the frequency with which pain prompts the patient to re-dose).

The problem of rapid offset of pain relief has promoted the development of sustained release technologies. Such technologies include transdermal patches and sublingual tablets. However, transdermal patches can cause skin irritation and the drug dosage is difficult to control. Sublingual tablets have an unpleasant taste and must be maintained in the mouth for relatively long periods of time (often 30 minutes or more), leading to compliance problems.

However, the principal problem associated with such sustained analgesia techniques stems from the fact that the onset of pain relief is slow and associated with a lag time of at least an hour (during which plasma levels of the analgesic steadily climb towards the therapeutic concentration threshold). In many applications (especially in cases where pain is intense and prolonged) such pain relief dynamics are unacceptable.

There is therefore a need for pain relief that is both rapid onset as well as prolonged.

It has now been discovered that rapid onset and prolonged pain relief can be achieved by intranasal delivery of an analgesic composition. This discovery is surprising in view of the existence of the so-called "rapid mucociliary clearance mechanism", which removes

deposited material from the front of the nose to the throat with a half-time of about 10 to 20 minutes.

Summary of the Invention

According to the invention there is provided an intranasal analgesic composition comprising in combination an analgesic component and a delivery agent, whereby on introduction into the nasal cavity of a patient to be treated the analgesic component is delivered to the bloodstream by the delivery agent to produce rapid onset and prolonged analgesia.

The analgesic delivery profile of the present invention may also avoid the relatively high C_{max} values associated with IV administration and so lead to an improved therapeutic index. It may also permit reduction (or elimination) of some or all of the side effects associated with the analgesic.

In preferred embodiments, the delivery agent is adapted to deliver the analgesic component such that $C_{max} = C_{opt}$.

Preferably, the delivery agent delivers the analgesic component such that C_{ther} is attained within 30 minutes (for example within 0.5 to 20.0 minutes, e.g. 0.5 to 15.0 minutes) after introduction into the nasal cavity. The delivery agent may be adapted to deliver the analgesic component such that T_{maint} is 6 to 24 hours. For example, the delivery agent may be adapted to deliver the analgesic component such that T_{maint} is 6 to 12 hours, 7 to 12 hours, 8 to 12 hours, 9 to 12 hours, 10 to 12 hours or 11 to 12 hours.

Any analgesic may be used according to the present invention, including any of the opioid, NSAID, Cox-2 inhibitors, tricyclic antidepressants, anticonvulsants and antimigraine compounds described above in the section entitled "Background to the Invention".

Preferably, the analgesic is an opioid.

Preferred opioid analgesics include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene,

dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalbuphine, nalorphine, naloxone, naltrexone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, profadol, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol and esters, salts and mixtures of any of the foregoing. The opioid analgesic may comprise mixed *mu*-agonists/antagonists, *mu*-antagonist combinations and esters, salts and mixtures thereof.

Particularly preferred is buprenorphine.

In another aspect the invention contemplates methods for producing rapid onset and prolonged analgesia comprising the steps of intranasally administering the composition of the invention to a patient experiencing pain.

The methods of the invention may involve multiple dosing. For example, the rapid onset analgesia produced by the compositions of the invention may permit self-titration of analgesic by the patient: the analgesic effect of an initial dose can be quickly and reliably gauged by the patient and if insufficient can be immediately supplemented by further dose(s) (often alternating between each nostril) until the required level of analgesia is attained. Multiple dosing may also be used in order to extend pain relief beyond the T_{maint} (especially in cases where the T_{maint} is relatively short). For example, in cases where T_{maint} is about 6 hours, multiple dosing (about 2 to 4 times a day) may be indicated. Where T_{maint} is about 12 hours, dosing about 2 times a day may be sufficient.

The compositions of the invention may be used in therapy or prophylaxis and accordingly may be packaged or presented for such use.

The therapy or prophylaxis may involve the treatment or management of chronic or acute pain, for example the management of peri-operative pain (e.g. abdominal surgery, back surgery, caesarean section, hip replacement or knee replacement).

Other medical uses include: pre-operative intranasal administration of the composition; therapy or prophylaxis adjunctive to anesthesia; post-operative analgesia; the

management of trauma pain; the management of cancer pain; the management of endometriosis; the management of inflammatory pain; the management of arthritis pain (including pain associated with rheumatoid arthritis and osteoarthritis); the management of back pain; the management of myocardial pain (for example ischaemic or infarction pain); the management of dental pain; the management of neuropathic pain (e.g. diabetic neuropathy, post-herpetic neuralgia or trigeminal neuralgia); the management of colic (e.g. renal colic or gallstones), headache, migraine, fibromyalgia or dysmenorrhoea; the management of breakthrough pain associated with malignant and non-malignant disease.

Preferably, the therapy or prophylaxis is not associated with nausea and/or vomiting and/or constipation and/or addiction and/or sedation.

The invention contemplates a nasal drug delivery device comprising the compositions of the invention.

The delivery agent used in the compositions of the invention may comprise (or consist of) an absorption promoting agent. Preferred are mucosal adhesive, for example bioadhesives selected from cationic polymers, surface active agents, fatty acids, chelating agents, mucolytic agents, cyclodextrins, diethylaminoethyl-dextran (DEAE-dextran) or combinations thereof.

Particularly preferred is chitosan, as defined herein.

In embodiments where chitosan is used, it may be present in combination with pectin and/or other gelling and/or viscosity enhancing agents.

When used, the pectin is preferably a low DE pectin.

The delivery agent may also comprise (or consist of) liposomes, powders, particles, microspheres or combinations thereof.

The composition may take the form of an emulsion. Such formulations may be preferred where the analgesic component is not readily soluble in water. Preferably, the emulsion is an oil-in-water emulsion. Particularly preferred are oil-in-water emulsions wherein the oil phase of the emulsion comprises a hydroxylated oil.

The delivery agent may comprise liposomes encapsulating one or more of the analgesic component(s), as described *infra*.

Processes for the manufacture or formulation of intranasal compositions are also contemplated by the invention.

Detailed Description of the Invention

Definitions

Where used herein and unless specifically indicated otherwise, the following terms are intended to have the following meanings in addition to any broader (or narrower) meanings the terms might enjoy in the art:

The term *analgesic* is used herein to define a pharmaceutical agent that can ameliorate or eliminate pain when administered to a patient.

The term *intranasal* in relation to drug delivery is used herein to indicate that the drug is delivered *via* the nose (usually one or more of the nostril(s)). The term therefore encompasses all forms of pernasal drug delivery (i.e. all forms of drug delivery performed through the nose). Thus, intranasal drug delivery as defined herein results in delivery of the drug to the nasal cavity (for example, to one or both halves thereof).

The term *dose-response curve* defines the relationship between the dose of any given analgesic and its analgesic effect or side-effects. The dose-response curve for analgesia is often displaced to the left with respect to the dose-response curve for side-effects, such that doses that produce analgesia may be lower than doses that produce unacceptable side-effects. Hence, by limiting plasma levels to those that produce analgesia without unacceptable side-effects, it may be possible to improve therapeutic index.

The term *rapid onset analgesia* is used herein to indicate pain relief that follows administration of the analgesic within 30 minutes.

The term *prolonged analgesia* is used herein to indicate pain relief that is maintained for at least 6 hours after administration of the analgesic.

The term C_{max} defines the peak plasma concentration of the analgesic attained after administration.

The term C_{opt} is used herein in relation to analgesic drugs which exhibit a dose-response curve for analgesia which is displaced to the left with respect to the dose-response curve for side-effects, to define a therapeutic plasma concentration or range thereof which produces acceptable pain relief or pain amelioration but which does not produce side-effects or produces side effects which are less than those associated with higher plasma concentrations.

The term T_{max} defines the time interval after administration of the analgesic at which C_{max} occurs.

The term C_{ther} defines a *therapeutic plasma concentration or range thereof*. Thus, the term is used herein to define a blood plasma concentration (or range of plasma concentrations) of the analgesic (or its bioactive metabolite) that produces pain relief or pain amelioration.

The term T_{maint} defines the duration of maintenance of C_{ther} after administration of the analgesic.

The term *opioid* is used herein to define drugs with morphine-like properties.

The term *buprenorphine*, unless otherwise indicated, is used as a term of art having the meaning normally attached to it by those skilled in the art and the term is therefore intended to cover all pharmaceutically acceptable salts, esters or free bases of the buprenorphine drug having the formula set out *infra*.

Posology

The compositions of the present invention are administered by nasal administration.

Nasal administration of drugs can be an effective and safe route of drug delivery. The highly permeable tissue of the nasal cavity can quickly absorb applied drugs, often more efficiently than tableted forms. Nasal drug delivery is less painful and invasive than injections and so is usually associated with less anxiety and greater compliance. Drugs delivered nasally bypass first pass metabolism and so may be administered in smaller

doses than medication delivered in tablet form. Inter-patient variability (seen often with certain opioids including buprenorphine) is also reduced.

A wide range of nasal delivery devices are available that allow drugs to be administered in precise, metered doses. This permits drug administration by doctors, nurses or even the patients themselves. Such devices also do not produce the bio-hazardous waste associated with syringe needles.

The amount of analgesic administered can vary widely according to the particular dosage unit employed, the period of treatment, the age and sex of the patient treated, the nature and extent of the pain treated, and the particular analgesic selected.

Moreover, in some embodiments the analgesic component can be used in conjunction with other agents known to be useful in the treatment of pain and/or inflammation and in such embodiments the dose may be adjusted accordingly.

However, typical doses for buprenorphine may be between 0.2 and 1.2 mg (e.g. between 0.2 and 0.6 mg).

The invention contemplates the composition of the invention together with (e.g. contained within) a device adapted for intranasal delivery (for example, a nasal insufflator device). Such devices are already in use for commercial powder systems intended for nasal application (e.g. Fisons' Lomudal™ System).

When used according to the present invention, the insufflator may be used to produce a fine, dispersed plume of the dry powder or microspheres. The insufflator is preferably provided with means for administering a predetermined dose of the analgesic composition. Powder or microspheres may be contained in a bottle or container adapted to be used with the insufflator. Alternatively, powders or microspheres may be provided in capsules (e.g. gelatin capsules) or other single dose devices adapted for nasal administration, in which embodiments the insufflator may comprise means for breaking open the capsule (or other single dose device).

In cases where the composition of the invention is provided in the form of a solution or dispersion in an aqueous medium, it can be administered as a spray using an appropriate device such as a metered dose aerosol valve or a metered dose pump. Any suitable propellant (including gas or liquid propellants) can be used.

Details of other devices suitable for use with the present invention can be found for example in Bell, A. Intranasal Delivery Devices, in Drug Delivery Devices Fundamentals and Applications, Tyle P. (ed.), Dekker, New York, 1988 and in Remington's Pharmaceutical Sciences, Mack Publishing Co., 1975.

Formulation

The analgesic component of the compositions of the invention is provided in combination with a delivery agent. The delivery agent acts to deliver the analgesic compound to the bloodstream such that rapid onset and prolonged analgesia is obtained. Thus, the delivery agents of the invention act as an analgesic absorption modifier and any of a wide variety of delivery agents may be used providing that this functional requirement is met.

The delivery agent may comprise an absorption promoting agent. Such agents promote uptake of the analgesic component into the bloodstream. They may act *via* a variety of different mechanisms. Particularly preferred are mucosal adhesives. Such adhesives maintain an intimate association between the bulk analgesic composition and the nasal mucosa, so enhancing absorption and extending the T_{max} of the analgesic component. They can also be used to lower the analgesic C_{max}, which may be important in applications where the minimization or elimination of side-effects is desired.

Suitable absorption promoting agents include cationic polymers (particularly chitosans), surface active agents, fatty acids, chelating agents, mucolytic agents, cyclodextrins, diethylaminoethyl-dextran (DEAE-dextran; a polycationic derivative of dextran) or combinations thereof.

Chitosans

A preferred absorption promoting agent is chitosan. The term *chitosan* is used herein to cover chitosan and salts or derivatives thereof (including, without limitation, poly-N-acetyl-D-glucosamine, polyglucosamines and oligomers of glucosamine materials of different molecular weights, in which the greater proportion of the N-acetyl groups have been removed through hydrolytic deacetylation).

Preferably, the chitosan used according to the invention is produced from chitin by deacetylation to a degree of greater than 40%, preferably between 50% and 98%, and more preferably between 70% and 90%.

Suitable chitosan salts include without limitation nitrate, phosphate, sulphate, hydrochloride, glutamate, lactate or acetate salts. Suitable chitosan derivatives include without limitation ester, ether or other derivatives formed by bonding of acyl and/or alkyl groups with OH groups, but not the NH_2 groups, of chitosan. Examples are O-alkyl ethers of chitosan and O-acyl esters of chitosan. Chitosan derivatives for use in the invention include modified chitosans (for example chitosans conjugated to polyethylene glycol).

Low and medium viscosity chitosans (for example CL113, G210 and CL110) may be obtained from various sources, including Pronova Biopolymer, Drammen, Norway; Seigagaku America Inc., MD, USA; Meron (India) Pvt, Ltd., India; Vanson Ltd, VA, USA; and AMS Biotechnology Ltd., UK. Suitable derivatives include those described in Roberts, Chitin Chemistry, MacMillan Press Ltd., London (1992).

The chitosan, chitosan derivative or salt used according to the present invention may have an intrinsic viscosity of at least 400 ml/g (for example at least 500, 750 or 1000 ml/g) and may have a molecular weight of 4,000 Daltons or more (for example 25,000 to 2,000,000 Daltons). Particularly preferred are chitosan or chitosan derivatives having a molecular weight of 50,000 to 300,000 Daltons. Preferably, the chitosan or chitosan derivative is water-soluble.

Low molecular weight chitosans can be prepared by enzymatic digestion of chitosan using chitosanase or by chemical breakdown (for example by treatment with nitrous acid).

Particularly preferred for use in the present invention is deacetylated chitin, or poly-N-acetyl-D-glucosamine in the form of a solution or as microspheres.

In certain applications, the chitosan may advantageously be used in combination with pectins (see below) and/or other gelling and/or viscosity enhancing agents.

<u>Other cationic polymers</u>

Cationic polymers suitable for use as absorption promoting agents also include polycationic carbohydrates. The polycationic substances for use in the present invention

preferably have a molecular weight of 10 000 or more and may be used at concentrations of 0.01 to 50% w/v (preferably 0.1 to 50%, and more preferably 0.2 to 30%).

Examples of suitable polycationic polymers are polyaminoacids (e.g. polylysine), polyquaternary compounds, protamine, polyamine, DEAE-imine, polyvinylpyridine, polythiodiethyl-aminomethylethylene, polyhistidine, DEAE-methacrylate, DEAE-acrylamide, poly-p-aminostyrene, polyoxethane, co-polymethacrylates (e.g. copolymers of HPMA, N-(2-hydroxypropyl)-methacrylamide), GAFQUAT (see for example US 3,910,862) and polyamidoamines.

<u>Surface active agents</u>

Suitable surface active agents for use according to the present invention are bile salts (for example sodium deoxycholate and cholylsarcosine, a synthetic N-acyl conjugate of cholic acid with sarcosine [N-methylglycine]). Also suitable for use in the invention are bile salt derivatives (for example sodium tauro dihydrofusidate). Any of a wide range of non-ionic surfactants (e.g. polyoxyethylene-9 lauryl ether), phospholipids and lysophosphatidyl compounds (e.g. lysolecithin, lysophosphatidyl-ethanolamine, lysophosphatidylcholine, lysophosphatidylglycerol, lysophosphatidylserine and lysophosphatidic acid) may also be used. Water-soluble phospholipids may also be employed (e.g. short chain phosphatidylglycerol and phosphatidylcholines). The concentration of surface active agents used according to the invention varies according to the nature of the analgesic component and the physico-chemical properties of the surface active agent selected, but typical concentrations are in the range 0.02 to 10% w/v.

Particularly preferred surface active agents for use as absorption promoting materials are phospholipids and lysophosphatides (hydrolysis products of phospholipids), both of which form micellar structures.

<u>Pectins</u>

Pectins can act as absorption modifiers either alone or in conjunction with an absorption promoting agent (for example with the chitosans, as described above). Thus, they can be used to modify the kinetics of delivery of the analgesic component, and may be particularly useful for increasing T_{max} and so effecting sustained release of the analgesic into the bloodstream to provide prolonged analgesia.

The term "pectin" is used herein to define hemicellulose polymers rich in D-galacturonic acid. Many (but not all) are plant cell wall components. The term includes the so-called "true pectins", which are characterized by the presence of an O-(a-D-galacturonopyrano syl)-(1 -2)-L -rhamnopyranosyl linkage within the molecule.

The pectins may be subcategorized on the basis of their structural complexity. At one extreme are "simple pectins", which are galacturonans. At the other extreme are "complex pectins" exemplified by rhamnogalacturonan II, which contains at least 10 different monosaccharide components in the main chain or as a components of branches. Pectins of intermediate complexity (herein referred to as "mesocomplex pectins" contain alternate rhamnose and galacturonic acid units, while others have branches of glucoronic acid linked to galacturonic acid.

Complex and mesocomplex pectins are made up of "smooth" regions (based on linear homogalacturonan) and "hairy" regions corresponding to the rhamnogalacturonan backbone with side-branches of varying length.

Certain pectins (for example, pectins obtainable from representatives of the plant family Chenopodiaceae, which include beets (e.g., sugar beet), spinach and mangelwurzels) are substituted to some extent with substituents derived from carboxylic acids (usually substituted cinnamic acids) containing phenolic groups.

An important property of pectins for use according to the present invention is the degree of esterification (DE) of the galacturonic acid units. The term "DE" as applied to pectins is a term of art and may be defined as the percentage of the total number of carboxyl groups which are esterified (or the methoxyl content of the pectin). The respective theoretical maximum for each is 100% and 16% respectively, but the DE of naturally-occurring pectins varies over the range 60 to 90%.

As used herein the term "degree of esterification (DE)", as applied to the pectins of the invention, refers to the total number of esterified carboxyl groups. Low DE pectins (typically having less than 50% esterification) may be prepared by de-esterification (either enzymatic or by acid or ammonia treatment in alcohol).

Preferred for use as gelling and/or viscosity modifying agents according to the present invention are pectins with a low DE. As used herein, the term "low DE" as applied to

pectins is intended to define pectins having less than 50%, and more preferably less than 35 %, esterification of carboxyl groups.

Pectins with a low DE can be obtained from known sources, or can be obtained *via* de-esterification of high DE pectins, as described above.

When used in the compositions of the invention the pectin may be introduced by dissolving or dispersing the pectin together with the analgesic component in an aqueous system, thereby producing a solution, suspension or emulsion. Alternatively, the analgesic component may be dissolved or suspended in an oil and then dispersed into the aqueous pectin solution to form an emulsion.

Those skilled in the art will appreciate that the physical system selected will depend upon the dose and physico-chemical properties of the analgesic component. Those skilled in the art will also appreciate that the concentration of pectin used will depend *inter alia* upon the nature of the pectin, analgesic component(s) and any other components (such as bioadhesives) present, but when present pectin will typically be present at concentrations of 1 to 100 g/L (for example 1 to 50 g/L, e.g. 2 to 10 g/L). Particularly preferred are analgesic compositions in which the pectin is present at a concentration of 5 to 10 g/L.

The intranasal compositions of the invention may be formulated in various physical forms, since the performance of the delivery agent may depend not only on its chemical attributes but also on its physical structure or milieu. For example, the delivery agent may constitute a physical structure that has a functional role in delivering the analgesic component to the bloodstream (for example where the delivery agent comprises or consists of liposomes, powders, particles, microspheres or combinations thereof).

Thus, the compositions of the invention may take the form of microsphere preparations, emulsions, liposome-based compositions, solutions, dispersions or powders, as described below.

Use of microspheres

When microspheres are used they are preferably prepared from a biocompatible material that will gel in contact with the mucosal surface. Substantially uniform solid microspheres are preferred. Starch microspheres (crosslinked if necessary) are preferred.

Microspheres may also be prepared from starch derivatives, modified starches (such as amylodextrin), gelatin, albumin, collagen, dextran and dextran derivatives, polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid and derivatives thereof (such as benzyl and ethyl esters), gellan gum and derivatives thereof (such as benzyl and ethyl esters) and pectin and derivatives thereof (such as benzyl and ethyl esters). The term "derivative" covers *inter alia* esters and ethers of the parent compound, which can be functionalised (for example to incorporate ionic groups).

Any of a wide variety of commercially available starch derivatives may be used, including hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch, succinate derivatives of starch and grafted starches.

Suitable dextran derivatives include, diethylaminoethyl-dextran (DEAE-dextran), dextran sulphate, dextran methyl-benzylamide sulphonates, dextran methyl-benzylamide carboxylates, carboxymethyl dextran, diphosphonate dextran, dextran hydrazide, palmitoyldextran and dextran phosphate.

The preparation of microspheres for use according to the invention may be carried out by known processes, including emulsion and phase separation methods (see for example Davis et al., (Eds), "Microspheres and Drug Therapy", Elsevier Biomedical Press, 1984, which parts relating to microsphere preparation are incorporated herein by reference). For example, albumin microspheres may be made using the water-in-oil emulsification method where a dispersion of albumin in oil is produced by homogenization or stirring, with the addition if necessary of small amounts of an appropriate surface active agent.

The size of the microspheres is largely determined by the speed of stirring or the homogenization conditions. Agitation can be provided by a simple laboratory stirrer or by more sophisticated devices (such as microfluidizers or homogenisers). Emulsification techniques may also be used to produce starch microspheres (as described in GB 1518121 and EP 223303) and for the preparation of gelatin microspheres.

Proteinaceous microspheres may be prepared by coacervation methods. Such methods include simple or complex coacervation as well as phase separation techniques (using solvents or electrolyte solutions). Such methods are well known to those skilled in the art and details may be found in standard textbooks (for example Florence and Attwood, Physicochemical Principles of Pharmacy 2nd Ed., MacMillan Press, 1988, Chapter 8).

The microspheres may advantageously have controlled-release properties, which may be conferred by modifications of the microspheres (for example by controlling the degree of cross-linking or by the incorporation of excipients that alter the diffusional properties of the analgesic component). Alternatively, controlled release properties may be incorporated by exploiting ion-exchange chemistry (for example DEAE-dextran and chitosan are positively charged and can be used for an ion-exchange interaction with metabolites that are negatively charged).

The maximum amount of analgesic component that can be carried by the microspheres is termed the loading capacity. It is determined by the physico-chemical properties of the analgesic component and in particular its size and affinity for the matrix of the microspheres. High loading capacities can be achieved when the analgesic is incorporated into the microspheres during microsphere manufacture.

Microcapsules (which may be bioadhesive and which may also exhibit controlled release properties) may also be employed as an absorption promoting agent in the compositions of the invention. These microcapsules can be produced by a variety of methods. The surface of the capsule may be inherently adhesive or can be modified by standard coating methods known to those skilled in the art. Suitable coating materials include bioadhesive polymers such as polycarbophil, carbopol, DEAE-dextran, alginate, microcrystalline cellulose, dextran, polycarbophils and chitosan).

Use of emulsions

Oil-in-water formulations can provide for the effective nasal delivery of analgesics that are poorly soluble in water. In such applications nasal irritation may also be reduced.

The oil phase of the emulsions of the invention may comprise a hydroxylated oil, particularly a hydroxylated vegetable oil. As used herein the term "hydroxylated oil" is intended to cover any oil that contains hydroxylated fatty acids. Preferred hydroxylated oils are hydroxylated vegetable oils, and a preferred hydroxylated vegetable oil for use in the present composition is castor oil.

As used herein, the term "castor oil" is intended to include ricinus oil, oil of Palma Christie, tangantargon oil and Neoloid (as described in Merck Index, 12th Edition, p. 311), as well as the oil from Ricinus Zanzibarinus. The latter has a high content of

glycerides of ricinoleic acid. Thus, castor oil comprises glycerides of ricinoleic acid (a hydroxy fatty acid).

When castor oil is used in the present invention, it may conveniently be obtained by cold pressing of the seeds of Ricinus Communis L., (Fam. Euphorbiaceae).

The oil phase in the emulsions of the invention may constitute 1 to 50% v/v of the emulsion. A preferred concentration of oil in the emulsion is from 10 to 40% v/v. Particularly preferred are concentrations of 20 to 30% v/v.

The emulsion compositions of the invention can be prepared using conventional methods such as by homogenisation of a mixture of the oil and analgesic component with an aqueous phase (optionally together with a stabilizing agent). Any suitable device may be used, including a microfluidizer or ultrasonic device, though microfluidizers are preferred for large scale production.

Suitable stabilizers for use in the emulsions of the invention include block copolymers containing a polyoxyethylene block (i.e. a block made up of repeating ethylene oxide moieties). An example of a suitable stabilizer of this type is Poloxamer™. Other suitable stabilizers include phospholipid emulsifiers (for example soy and egg lecithins). Particularly preferred is the egg lecithin Lipoid E80™ (from Lipoid™), which contains both phosphatidylcholine and phosphatidylethanoline. Other suitable phospholipids include phospholipid-polyethylene glycol (PEG) conjugates (see for example Litzinger *et al.*, Biochem Biophys Acta, 1190 (1994) 99-107).

Any suitable concentration of stabilizer/emulsifier may be used, and it typically falls within the range 0.1 to 10% w/v in the aqueous phase of the emulsion. Particularly preferred are concentrations of 1 to 5% w/v.

The stability of the emulsion can be enhanced by the addition of one or more co-emulsifier(s). Suitable pharmaceutically-acceptable co-emulsifiers include fatty acids, bile acids and salts thereof. Preferred fatty acids have greater than 8 carbon atoms, and particularly preferred is oleic acid. Of the suitable bile acids, preferred is deoxycholic acid. Suitable salts pf the foregoing include the alkali metal (e.g. Na and K) salts. Co-emulsifiers can be added at a concentration of 1% w/v or less on the aqueous phase.

Buffering agents may also be used in the composition. For example, a buffer may used to maintain a pH that is compatible with nasal fluid, to preserve emulsion stability and/or to ensure that the analgesic component does not partition from the emulsion oil phase into the aqueous phase.

It will be clear to the person skilled in the art that additional components can also be added to the emulsion including thickening and gelling agents (such as cellulose polymers, particularly sodium carboxymethyl cellulose, alginates, gellans, pectins, acrylic polymers, agar-agar, gum tragacanth, gum xanthan, hydroxyethyl cellulose, chitosan, as well as block copolymers of polyoxyethylene-polyoxypropylene). Preservative agents such as methyl parabenzoates, benzylalcohol and chlorobutanol may also be added.

Use of liposomes

In some embodiments of the invention the delivery agent comprises or is a liposome.

Liposomes are microscopic vesicles composed of an aqueous compartment surrounded by a phospholipid bilayer that acts as a permeable entrapment barrier. Many different classes of liposomes are known (see Gregoriadis (ed.) in Liposome Technology, 2nd edition, vol I-III, CRC Press, Boca Ranto, Fla., 1993). Some liposomes can provide controlled sustained release of the encapsulated drug. In such systems, the rate of drug release is determined by the liposome's physicochemical properties. Liposomes can be tailored for a specific application by modification of size, composition, and surface charge to provide the desired rate of drug delivery (see Meisner D, et al: In Proceedings, 15th International Symposium on Controlled Release of Bioactive Materials. 15:262-263, 1988; Mezei M: In Drug Permeation Enhancement, Theory and Application. Hsieh DS (ed.): Marcel Dekker Inc., New York, 1993, pp 171-198; and Meisner D, et al: J Microencapsulation 6:379-387, 1989).

Thus, liposome-encapsulation can act as an effective and safe delivery agent in the compositions of the invention.

The sustained release property of the liposomal product can be regulated by the nature of the lipid membrane and by the inclusion of other excipients in the composition of the liposomal products. Current liposome technology permits a reasonable prediction on the rate of drug release based on the composition of the liposome formulation. The rate of drag release is primarily dependent on the nature of the phospholipids, e.g. hydrogenated

(-H) or unhydrogenated (-G), or the phospholipid/cholesterol ratio (the higher this ratio, the faster the rate of release), the hydrophilic/lipophilic properties of the active ingredients and by the method of liposome manufacturing.

Materials and procedures for forming liposomes are well known to those skilled in the art and include ethanol or ether injection methods. Typically, the lipid is dissolved in a solvent and the solvent evaporated (often under reduced pressure) to produce a thin film. The film is then hydrated with agitation. The analgesic component is incorporated at the lipid film forming stage (if lipophilic) or at the hydration phase as part of the aqueous hydrating phase (if hydrophilic). Depending on the hydration conditions selected and the physicochemical properties of the lipid(s) used, the liposomes can be multilamellar lipid vesicles (MLV), unilamellar lipid vesicles (including small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV)) and as multivesicular liposomes.

Lipid components typically comprise phospholipids and cholesterol while excipients may comprise tocopherol, antioxidants, viscosity inducing agents and/or preservatives. Phospholipids are particularly useful, such as those selected from the group consisting of phosphatidylchloines, lysophosphatidylchloines, phosphatidylserines, phosphatidylethanolamines, and phosphatidylinositols. Such phospholipids may be modified using, for example, cholesterols, stearylamines, stearic acid, and tocopherols.

Other components and formulations

The compositions of the invention may further comprise other suitable excipients, including for example inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc.

Excipients such as humectants, isotoning agents, antioxidants, buffers and/or preservatives are preferably used. Formulation and dosage would depend on whether the analgesic is to be used in the form of drops or as a spray (aerosol). Alternatively, suspensions, ointments and gels can be applied to the nasal cavity. However, it is known that nasal mucous membranes are also capable of tolerating slightly hypertonic solutions. Should a suspension or gel be desired instead of a solution, appropriate oily or gel

vehicles may be used or one or more polymeric materials may be included, which desirably should be capable of conferring bioadhesive characteristics to the vehicle.

Many other suitable pharmaceutically acceptable nasal carriers will be apparent to those skilled in the art. The choice of suitable carriers will depend on the exact nature of the particular nasal dosage form desired, for example whether the drug is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment or a nasal gel. In another embodiment, nasal dosage forms are solutions, suspensions and gels, which contain a major amount of water (preferably purified water) in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters (e.g. a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present.

The nasal compositions of the invention may be isotonic, i.e. have the same osmotic pressure as blood serum. If desired, sustained release nasal compositions, e.g. sustained release gels, can be readily prepared, preferably by employing the desired drug in one of its relatively insoluble forms, such as the free base or an insoluble salt.
The composition of the present invention may be adjusted, if necessary, to approximately the same osmotic pressure as that of the body fluids (i.e. isotonic). Hypertonic solutions can irritate the delicate nasal membranes, while isotonic compositions do not. Isotonicity can be achieved by adding glycerol or an ionic compound to the composition (for example, sodium chloride).

The compositions of the invention may take the form of a kit of parts, which kit may comprise the intranasal composition together with instructions for use and/or unit dosage containers and/or an intranasal delivery device.

Equivalents

The foregoing description details presently preferred embodiments of the present invention. Numerous modifications and variations in practice thereof are expected to occur to those skilled in the art upon consideration of these descriptions. Those modifications and variations are intended to be encompassed within the claims appended hereto.

CLAIMS:

1. An intranasal analgesic composition comprising in combination an analgesic component and a delivery agent, whereby on introduction into the nasal cavity of a patient to be treated the analgesic component is delivered to the bloodstream by the delivery agent to produce rapid onset and prolonged analgesia.
2. The composition of claim 1 wherein the delivery agent delivers the analgesic component such that C_{ther} is attained within 30 minutes (for example within 0.5 to 20, e.g. 0.5 to 15.0 minutes) after introduction into the nasal cavity.
3. The composition of claim 2 wherein C_{ther} is attained within 1.0 to 15.0 minutes after introduction into the nasal cavity.
4. The composition of claim 3 wherein C_{ther} is attained within 2.0 to 8.0 minutes after introduction into the nasal cavity.
5. The composition of claim 4 wherein C_{ther} is attained within 3.0 to 5.0 minutes after introduction into the nasal cavity.
6. The composition of any one of the preceding claims wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 24 hours.
7. The composition of claim 6 wherein the delivery agent delivers the analgesic component such that such that T_{maint} is 6 to 20 hours.
8. The composition of claim 7 wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 18 hours.
9. The composition of claim 8 wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 16 hours.
10. The composition of claim 9 wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 14 hours.
11. The composition of claim 10 wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 11 hours.
12. The composition of claim 11 wherein the delivery agent delivers the analgesic component such that T_{maint} is 6 to 10 hours.
13. The composition of any one of the preceding claims wherein the analgesic comprises an opioid.
14. The composition of claim 13 wherein the analgesic comprises (or consists of) buprenorphine.
15. The composition of claim 14 wherein C_{ther} is 0.4 ng/ml or greater.
16. The composition of claim 15 wherein C_{ther} is in the range 0.4 ng/ml to 5.0 ng/ml.
17. The composition of any one of claims 14 to 16 wherein C_{max} is 1 to 5 ng/ml.
18. The composition of claim 17 wherein C_{max} is 1 to 4 ng/ml.

19. The composition of claim 18 wherein C_{max} is 1 to 3 ng/ml (for example 1 to 2 ng/ml).

20. The composition of any one of the preceding claims wherein $C_{max} = C_{opt}$.

21. The composition of any one of claims 14 to 20 wherein C_{ther} during T_{maint} is 0.4 to 1.5 ng/ml.

22. The composition of claim 21 wherein C_{ther} during T_{maint} is 0.4 to 1.2 ng/ml.

23. The composition of claim 22 wherein C_{ther} during T_{maint} is 0.4 to 1.0 ng/ml.

24. The composition of claim 23 wherein C_{ther} during T_{maint} is 0.4 to 0.8 ng/ml.

25. The composition of claim 24 wherein C_{ther} during T_{maint} 0.4 to 0.6 ng/ml.

26. The composition of any one of the preceding claims for use in therapy or prophylaxis.

27. Use of the composition of any one of claims 1 to 25 for the manufacture of a medicament for intranasal use in therapy or prophylaxis.

28. The composition of claim 26 or use of claim 27 wherein the therapy or prophylaxis is the treatment or management of chronic or acute pain.

29. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of peri-operative pain (e.g. abdominal surgery, back surgery, caesarean section, hip replacement or knee replacement).

30. The composition or use of claim 29 wherein the therapy or prophylaxis comprises pre-operative intranasal administration of the composition.

31. The composition or use of claim 29 wherein the therapy or prophylaxis is adjunctive to anesthesia.

32. The composition or use of claim 29 wherein the therapy or prophylaxis comprises post-operative intranasal administration of the composition.

33. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of trauma pain.

34. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of cancer pain.

35. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of endometriosis.

36. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of inflammatory pain.

37. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of arthritis pain.

38. The composition or use of claim 37 wherein the therapy or prophylaxis is the management of pain associated with rheumatoid arthritis or osteoarthritis.

39. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of back pain.

40. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of myocardial pain, for example ischaemic or infarction pain.

41. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of dental pain.

42. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of neuropathic pain (e.g. diabetic neuropathy, post-herpetic neuralgia or trigeminal neuralgia).

43. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of colic (e.g. renal colic or gallstones), headache, migraine, fibromyalgia or dysmenorrhoea.

44. The composition or use of claim 28 wherein the therapy or prophylaxis is the management of breakthrough pain associated with malignant and non-malignant disease.

45. The composition or use of claim 28 wherein the therapy or prophylaxis is not associated with nausea and/or vomiting and/or constipation and/or addiction and/or sedation.

46. A nasal drug delivery device comprising the composition as defined in any one of the preceding claims.

47. A method for producing rapid onset and prolonged analgesia comprising the steps of intranasally administering the composition as defined in any one of claims 1 to 45 to a patient.

48. The method of claim 47 wherein the analgesia is the treatment or management of chronic or acute pain as defined in any one of claims 28 to 45.

49. The method of claim 47 or 48 wherein C_{ther} is attained within a period as defined in any one of claims 2 to 5.

50. The method of any one of claims 47 to 49 wherein T_{maint} is as defined in any one of claims 6 to 12.

51. The method of any one of claims 47 to 50 wherein the analgesic comprises (or consists of) buprenorphine and C_{ther} is as defined in claim 15 or 16.

52. The method of any one of claims 47 to 51 wherein the analgesic comprises (or consists of) buprenorphine and C_{max} is as defined in any one of claims 17 to 20.

53. The method of any one of claims 47 to 52 wherein the analgesic comprises (or consists of) buprenorphine and wherein C_{ther} during T_{maint} is as defined in any one of claims 21 to 25.

54. The composition, use or method of any one of the preceding claims wherein the delivery agent comprises (or consists of) an absorption promoting agent.
55. The composition, use or method of claim 54 wherein the absorption promoting agent comprises a mucosal adhesive.
56. The composition, use or method of claim 55 wherein the mucosal adhesive is selected from: cationic polymers, surface active agents, fatty acids, chelating agents, mucolytic agents, cyclodextrins, diethylaminoethyl-dextran (DEAE-dextran) or combinations thereof.
57. The composition, use or method of claim 56 wherein the mucosal adhesive is chitosan.
58. The composition, use or method of claim 57 wherein the chitosan is in combination with pectin and/or other gelling and/or viscosity enhancing agents.
59. The composition, use or method of claim 58 wherein the pectin is a low DE pectin.
60. The composition, use or method of any one of the preceding claims wherein the delivery agent comprises (or consists of) liposomes, powders, particles, microspheres or combinations thereof.
61. The composition, use or method of any one of claims 1 to 60 wherein the composition is in the form of an emulsion.
62. The composition, use or method of claim 61 wherein the emulsion is an oil-in-water emulsion.
63. The composition, use or method of claim 62 wherein the oil phase of the emulsion comprises a hydroxylated oil.
64. The composition, use or method of claim 60 wherein the liposomes encapsulate one or more of the analgesic component(s).